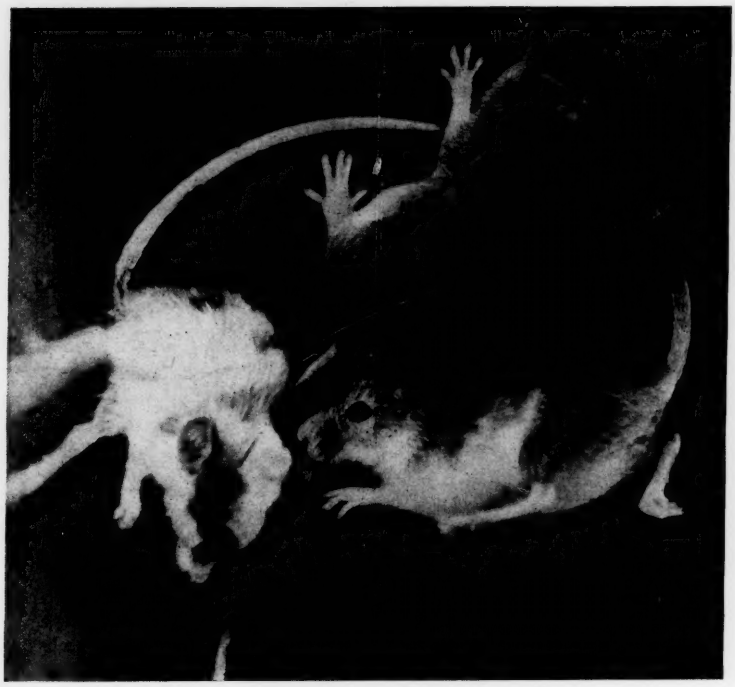
The Journal of HEREDITY



"JITTERY" TABLEAU

(SEE PAGE 279)

SPECIAL "JAX-MOUSE" ISSUE

The "Varitint-Waddler"
A Chromosome Map of the Mouse
"Misty" and "Belted" — New Coat-Color Genes
"Jittery" and "Pirouette" — Two New "Waltzing" Genes
Abnormal Mammae in Inbred Strains Detection of Mutations

VOLUME 36 SEPTEMBER, 1945 NUMBER 9

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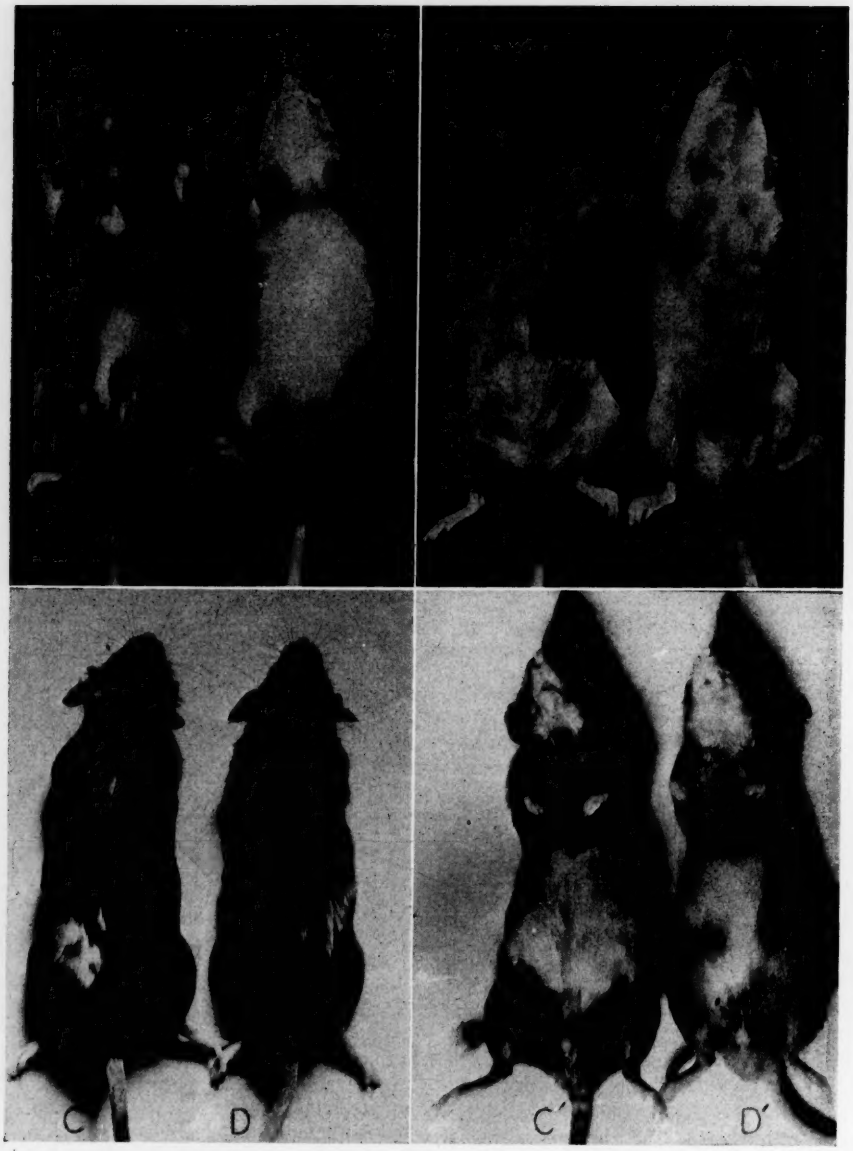
From the Roscoe B. Jackson Memorial Laboratory

THIS special "Jax" Mouse issue emphasizes the multidependent nature of science. The main objective of the Roscoe B. Jackson Memorial Laboratory is to conduct research to determine the causes of cancer, and to facilitate similar research in other institutions. One of the outstanding achievements of the Laboratory has been the production of a large number of highly inbred strains of mice. These standardized "Jax" mice are the basic raw material for a great many important researches in the biology, physiology, and chemistry of cancer in scores of laboratories in the U. S. and abroad. The production of uniform strains was a primary essential to studying the genetic component of cancer, but it has also been invaluable to workers attacking other aspects of this multiplex problem. The inbred strains of mice are being maintained in sufficient quantity so that during 1944-45 over 300,000 animals were made available for scientific research in laboratories throughout the United States, both for private research and for the war effort.

The work of the Laboratory is based principally on the genetic approach. Most of the known Mendelian mutant varieties of mice are maintained. Problems of growth, both normal and ab-

(*Continued on page* 271)



NEW AND OLD DOMINANT SPOTTINGS COMPARED

Figure 1

A and *A′*—Dorsal and ventral views of the varitint-waddler mutation. Note the three-toned effect. *B* and *B′*—A Mouse heterozygous for both varitint-waddler and dominant spotting (of the genotype *VavaWw*). *C* and *C′*—Dominant spotting (*W*); *D* and *D′*—Viable dominant spotting (W^v). Note the general lightening of the coat in the latter. Both mice are non-agouti (*aa*). The *W* gene produces a fatal anemia, while the *Va* mice are deaf, subject to convulsive seizures, and unable to swim.

THE VARITINT-WADDLER MOUSE

A Dominant Mutation in Mus Musculus*

ARTHUR M. CLOUDMAN AND LESTER E. BUNKER, JR.

A VARITINT-WADDLER mouse is just what the name implies. Its coat is variously tinted in color and all such individuals have a "duck like" walk. The origin and nature of this new character-complex is described below.

The JAX C57 black and JAX C57 brown stocks have been separated by over 100 generations of inbreeding. A cross between these stocks in 1942 produced normal appearing first generation hybrid young. A group of these F_1 hybrid females were backcrossed to males of the C57 black parent stock. One such backcross mating produced an exceptional male in a first litter of eight young and one offspring out of eight in the second litter was phenotypically of the same type. The same two parents produced a total of 26 young. There were 24 self black and two of these new type individuals.

Presumably the parents of these 26 young were of the genetic formulae *aaBb* and *aaBB* with respect to coat color. Numerous matings between this same *aaBB* father and three *aaBb* sisters of the mother produced only self black young. The two new individuals were different from their normal siblings in their morphology and behavior.

Preliminary data from crosses involving this new character revealed certain peculiarities of color and behavior that were characteristic. The two mutant individuals were heterozygous for the new factor and their color immediately suggested the descriptive term "variegation." However, this name was commonly used for phenotypic classifications of spotting[3,2] and the authors wished to avoid the confusion that might follow if "variegation" were employed for a new genetic classification. Since "varitint" is equally descriptive of the coat of these mutant mice it was chosen as a more suitable name.

All varitint mice, whether heterozygous or homozygous, are deaf, nervous, restless and excitable. Choreic head movements with waddling and "mixed" circling habits are present as early as 14 days after birth. "Varitint-waddler" (genetic symbol *Va*) has been selected for the name of the new character to cover both the coat character and the choreic actions.

VaVa mice are white except for small patches of unaltered color, usually near the ears and the base of the tail. At birth these animals are very pale.

The *Vava* mouse is detectable about three days after it is born, when scattered white areas appear on the head and body. Later these areas show white fur and the pigmented regions present bizarre color arrangements and gradations. The *Vava* individual has two separate and distinct expressions of the expected coat color (Figure 1*A* and *A'*).

Scattered mostly over the dorsal and lateral surfaces there may be one or several, small or large, islands of normally pigmented fur. These spots apparently remain unchanged throughout life. They are on a background of a paler tint of the same color. This background gets progressively paler with age. The fur of the *Vava* mice eventually becomes white, or nearly so, except for the unchanging colored spots. Nearly the entire ventral surface is white, even in young mice, but fully pigmented areas occasionally extend to the midventral line. The white spotting seen at three days has a very

*This work has been aided by grants to the Roscoe B. Jackson Memorial Laboratory from the Commonwealth Fund, Anna Fuller Fund, International Cancer Research Foundation, Jane Coffin Childs Memorial Fund and the National Advisory Cancer Council.

broken pattern. Sometimes there is an intermingling of white and colored hairs giving an appearance that might be called roan.

The choreic tendency varies in intensity in the *VaVa* and the *Vava* mice. For this reason a short description of their nervous reactions is given here. At about 14 days the *VaVa* individuals are extremely excitable. They are deaf but when their box is moved or they are disturbed by a sudden jarring they react quickly and violently. Usually they begin by rolling over and over. This is followed by jumping four or five inches into the air in rapid, wild, spasmodic leaps and finally ends with a convulsive stiffening of the body similar to jittery.[1] Such a convulsion leaves a mouse exhausted and may account for the loss of many *VaVa* animals under one month of age. The *Vava* individuals are not as excitable as the homozygotes and do not show a tendency to roll or leap, otherwise both types act very much alike. They are usually in motion when not asleep, nodding and tossing their heads. When walking they waddle and when excited they run in circles sometimes clockwise and sometimes counter clockwise. When placed in a glass jar some *Va* mice will jump into the air and turn over in a perpendicular circling motion.

With the exception of one female, all *VaVa* mice tested have been sterile. Some of the *Vava* mice, especially the males, are sterile. The females often make poor mothers because they neglect their young and trample them to death.

Crosses Made

The crosses discussed here show the behavior of varitint-waddler when crossed with:

(1) self
(2) piebald (*vava wwss*)
(3) the dominant spotting alleles *Ww vava SS* and W^vw *vava SS*.

The *W* gene and its behavior have been discussed by several authors.[4,9,11] Its allele W^v was first reported by Little and Cloudman.[10] The behavior of W^v has been further studied in relation to anemia.[5,6] In order to compare *Va* with *W* and its allele W^v these characters are shown in Figure 1. A *vava Ww aa* mouse is shown in Figure 1*C* and 1*C'* and a *vava* W^vw *aa* mouse in 1*D-D'*. This demonstrates the characteristic dilution of the coat pigment in *vava* W^vw *aa*. Both *vava Ww aa* and *vava* W^vw *aa* are phenotypically distinguishable from each other and also from *Vava ww aa* shown in Figure 1*A-A'*. The appearance of a small amount of pigment in the fur, especially at the base of the tail and about the head, makes *VaVa wwaa* mice different in appearance from both *vava WWaa* and *vava* W^vW^v *aa* individuals which are all white with black eyes. The anemia reported for mice of the *WW* and W^vW^v types[5,6] is not found in *VaVa* mice.

Experimental

The behavior of *Vava* when crossed with self (*vava*) has been tested with a number of different stocks. Since to date the findings have been uniform we have lumped the data from 93 litters (Table I). Out of 665 classified young there were 325 of the *Vava* type, and 340 self mice (*vava*). This is not significantly different from a 1:1 ratio indicating that one genetic factor is involved.

The results of *inter-se* crossing of *Vava* mice were based upon data from 62 litters. As mentioned before, *Vava* type females were so nervously active that many litters were lost soon after birth. Table I showed a total of 386 young that lived long enough to be classified. Of these young there were 18 *VaVa*, 236 *Vava* and 132 *vava* individuals. This was quite different from the ratio of 96.5 : 192 : 96.5 that would have been expected for 386 mice to make it consistent with the data from the first cross presented above.

It was obvious that the number of *VaVa* individuals observed was much less than expected on the basis of a single allele difference. We concluded that there was a high differential mortality for the homozygous varitint-waddler (*VaVa*) individuals. For this reason a second expected ratio was tabulated omitting the *VaVa* type. Here we

found that there was no significant deviation from a 2:1 ratio. This failure of many of the *VaVa* individuals to survive must have been associated with some developmental condition which eliminated many of this type quite early in embryonic life. As supporting evidence in favor of this theory we found that the average litter size from *Vava* × *Vava* matings was less than the average litter sizes from matings of either *Vava* × self or self × self. Siblings of *Vava* mice were used for self × self matings. It was clear (Table I) that *Va* acted as a dominant spotting character and was transmitted by a single gene. All of the segregants with either *VaVa* or *Vava* showed definite choreic actions. The self siblings failed to show this behavior. Not a single case of segregation between varitint and waddler was observed.

Crosses involving varitint-waddler and piebald were not extensive but the findings deserve mention. In the *Vava Ss* × *vava ss* cross early observations showed that either the segregants *Vava Ss* and *Vava ss* were phenotypically difficult to separate or that there was a definite preponderance of *Vava ss* mice. The majority in this class were not satisfactorily classified. For this reason the two classes were lumped in Table II. The presence of a number of self colored (*vava Ss*) mice showed that varitint-waddler and piebald were not alleles. Larger numbers of mice are being gathered for linkage tests.

Crosses involving varitint-waddler and the dominant spotting alleles *W* and W^v were made (Tables III and IV). In the *Vava ww* × *vava Ww* cross the double heterozygote class *Vava Ww* was nearly white except for some spots on the head and near the tail. This is shown in Figures 1*B* and 1*B'*. There was little difference phenotypically between this type of mouse and the *Vava* W^vw type (Table IV). Both of the double heterozygote classes were fertile. When either class was crossed with self, all four classes of segregants were recovered in a 1:1:1:1 ratio. These data showed that varitint-waddler was not an allele of dominant spotting and there was no evidence of linkage.

Discussion

The varitint-waddler mutation occurred twice and in different litters from the same parents. There is a definite probability that it arose through a change in the germ cells of the mother. Had the male been the one whose germ cells had changed, the mutation probably would have appeared in the offspring from matings with other females. The findings here strongly suggested that a small segment of one ovary of the mother had changed in some manner and was producing germ cells of the *VaBa* and *Vaba* types. The majority of the ova would have carried the expected *vaBa* and *vaba* genes. Since the mutation was a dominant the character would show up in matings involving the parent whose germ cells had changed.

The differential mortality of the *VaVa* type of mice and the sterility of most of them as well as of many *Vava* individuals may be associated with the nervous symptoms characterizing these mutants. Even if we consider the sterility to be secondary, we still have good evidence that a change in a single gene has affected very diverse parts of the organism. Since pigment presumably comes from the neural crest a single predisposing factor might operate quite early in embryonic development to affect the integument and the nervous system. The disturbances of hearing, equilibrium and pigment formation might conceivably be related in their early embryonic origin. One disconcerting element in the pigment change is the lack of uniformity in different areas. Some regions remain unaltered and are indistinguishable in themselves from self colored fur while adjacent areas exhibit a progressive paleing. These unaltered areas of pigmentation in a *Vava* mouse appear to be centrally delimited by the dorso-ventral mid-axis of the body. In other words if two lines were drawn, one dorsally and one ventrally, both extending from the tip of the nose to the base of the tail these pigmented spots would rarely if

ever extend across these lines. The significance of this is not clear but it appears to hold true for the mice observed. On the dorsal and lateral surfaces the background color has no characteristic delimitations. It may be that the effect of the *Va* gene begins at a time when some skin foci escape its influence but most of the skin either forms no pigment or the cells function imperfectly in pigment formation.

Among the inherited choreas[7] found in mice, waltzer, shaker-1, shaker-2, shaker-short, jerker, jittery,[1] fidget,[2] pirouette[12] and Bochum circle[7] all are recessive. All of them have a certain resemblance to each other and to varitint-waddler. Affected mice exhibit certain erratic movements in common and most of them have an associated deafness. *Va* differs from all the others in being a dominant character.

Table I. Crosses involving varitint-waddler and self

Crosses		VaVa	Vava	vava	total	young lost	No. of Lit.	Av lit size
Vava x vava	observed	0	325.0	340.0	665	32*	93	7.5
	expected (1:1)	0	332.5	332.5				
Vava x Vava	observed	18.0	236.0	132.0	386	37*	62	6.8
	expected(1:2:1)	96.5	192.0	96.5	386			
Omitting VaVa	" (2:1)	0	245.3	122.7	368			
vava x vava	observed	0	0	52	52	0	7	7.4
	expected	0	0	52	52			

* Unclassified and not included in the totals

Table II. Crosses involving varitint-waddler and piebald

Crosses	Vava (Ss and Ss-ss)	vava Ss	vava ss	total	young lost	No. lit.	Av.Lit size
Vava SS x vava ss observed	8.0	7.0	0	15	2*	2	8.5
expected(1:1)	7.5	7.5	0	15			
Vava Ss x vava ss observed	10.0	8.0	20.0	38	2*	5	8
expected (2:1:1)	19.0	9.5	9.5	38			

* Unclassified and not included in totals

Table III Crosses involving varitint-waddler and black-eyed white (*W*)

Crosses	Vava Ww	Vava ww	vava ww	vava Ww	total	young lost	no. lit	av.lit
Vava ww x vava Ww observed	36.0	71.0	80.0	49.0	236	15*	37	6.8
expected (1:1:1:1)	59.0	59.0	59.0	59.0	236			
Vava Ww x vava ww observed	6.0	10.0	11.0	11.0	38	4*	6	7.0
expected (1:1:1:1)	9.5	9.5	9.5	9.5	38			

* Unclassified and not included in totals

Table IV Crosses involving varitint-waddler and viable black-eyed white (W^V)

Crosses	VavaW^Vw	Vava ww	vava ww	vavaW^Vw	total	young lost	no. lit	av.lit
Vava ww x vava W^Vw observed	66.00	58.00	63.00	64.00	251	22*	40	6.8
expected(1:1:1:1)	62.75	62.75	62.75	62.75	251			
Vava W^Vw x vava ww observed	41.00	35.00	41.00	26.00	143	9*	23	6.6
expected (1:1:1:1)	35.75	35.75	35.75	35.75				

*Unclassified and not included in totals

The literature shows that some of these homozygous recessives were tested for swimming and sank to the bottom. *VaVa* mice placed in water rolled over and over and finally sank. The *Vava* mice swam easily in small circles. Preliminary tests showed that varitint-waddler, like waltzer, can be spun rapidly without getting dizzy. This dominant choreic action of *Va* cannot be separated from the pigment effects. The entire syndrome appears to be due to a single gene.

In the data from the matings of *Vava Ss* × *vava ss* mice there appears to be an excess of piebald mice. This may be due to the action of the "*k* genes."[4] A more extensive investigation would be needed to clarify this recessive spotting angle.

Summary

A new coat color, varitint-waddler (*Va*) was observed in an outcross between C57 black and C57 brown stocks. This pigment-altering character is expressed by coat modifications of three types: (1) many areas without pigmentation (2) large fields with partial and progressive suppression or dilution of color and (3) islands of unchanging coat pigmentation that are of the same color and intensity that is found in self siblings. There is always an associated choreic action. These two characters are probably due to the effect of a single gene that behaves as a simple dominant.

There is a high differential mortality in *VaVa* mice in embryonic life. The *VaVa* and *Vava* individuals that have been tested shown no anemia.

Matings were carried out which showed that varitint-waddler is not an allele of piebald. It has also been shown that *Va* is not an allele of the dominant spotting genes *W* and W^v. There is no evidence of linkage between varitint-waddler and dominant spotting.

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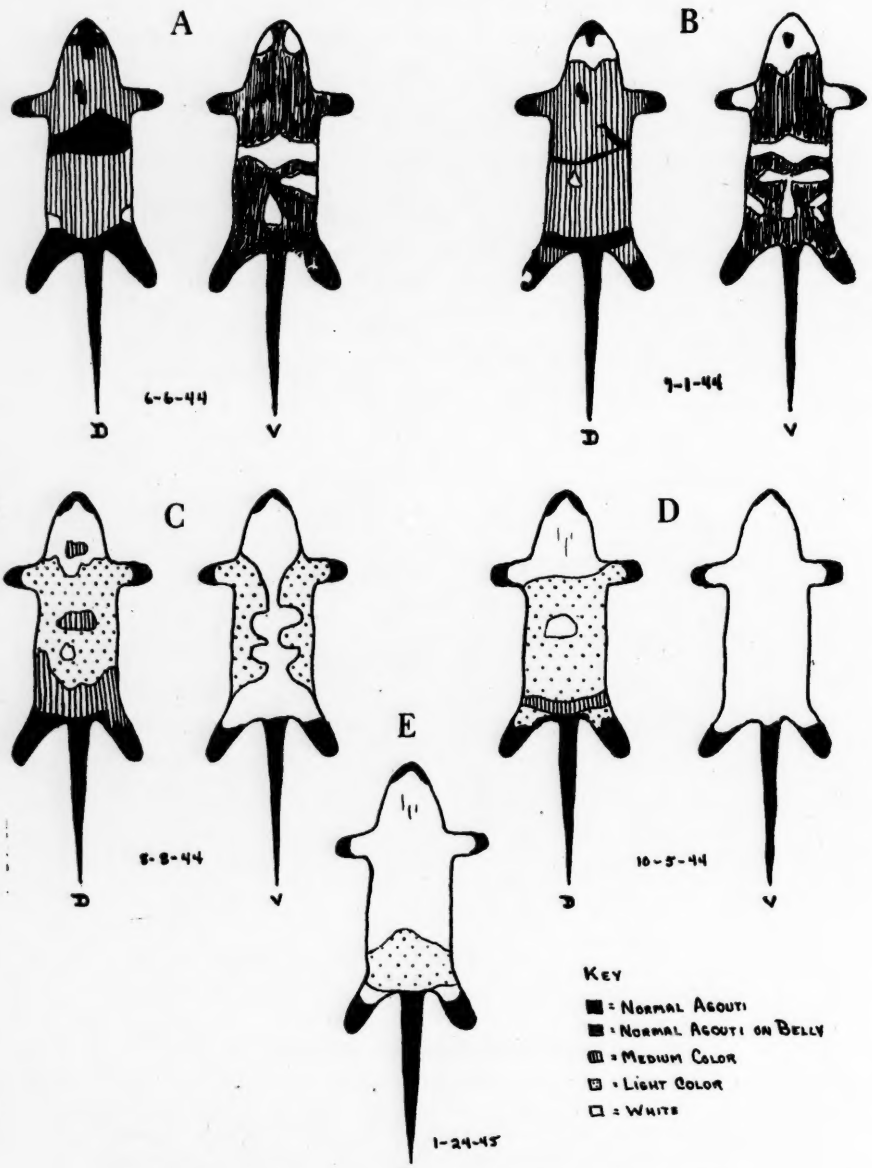
✦

Request for Seeds of Pawpaw

In order to complete a cytotaxonomic survey of the pawpaw, *Asimina triloba* (L.) Dun., Dr. Wray M. Bowden, University of Toronto, Toronto, Ontario, Canada, will appreciate the collection of a dozen viable seeds from every possible locality throughout the species area (New York to Florida, Nebraska to Texas). Seeds and a note on the locality of collection may be sent directly by letter.



PROGRESSION OF COLOR CHANGE IN "HIMALAYAN" MOUSE

Figure 2

A—Dorsal (*D*) and ventral (*V*) coat patterns of mouse when change was first noted. *B*—pattern a month later; *C*—two months later; *D*—four months later, belly now completely white; *E*—at twelve months of age, seven months after change started, only the ears and extremities are pigmented.

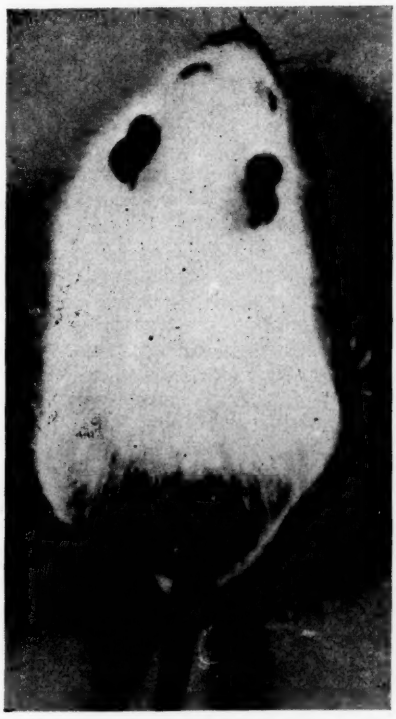
A UNIQUE "HIMALAYAN" MOUSE

MARGARET M. DICKIE*

IN June 1944, in an F_1 generation of a cross between two inbred strains—JAX strain A ♀ (*aabbcc*) × JAX strain C3H ♂ (*AABBCC*)—one male mouse five months old appeared to be moulting in a peculiar manner. The new hair was coming in one shade lighter than the original black agouti coat expected in such a heterozygous mouse (*AaBbCc*). Several white belly spots also became evident (Figure 2*A*) at the same time. This mouse (No. 2129) was closely observed for three months during which time the coat became progressively lighter (Figure 2*B* and *C*). Finally the entire belly became white (Figure 2*D*). The nose, ears, tail and feet remained normal in color the entire time. The diagrams shown give some idea of the progression of the color change.

At present, the mouse is one year old and in good health. He is now practically all white except for a yellow gray spot on his back that is slowly disappearing (Figure 2*E* and Figure 3). At all times the mouse has seemed very healthy and well nourished. He has always had a normal heavy coat.

Examination of the parents' record shows that of the total eighteen mice weaned, only this mouse has changed color. Crosses have been made to see whether the change is of an hereditary nature, or whether it is due to a singular physiological condition peculiar to this mouse. This male has been mated with a C3H female and with a JAX strain C57 black female (*aaBBCC*), and has been backcrossed with the offspring thus secured in an attempt to recover animals of the original type. Colors of the progeny, eight black agouti, one black, one brown agouti and two white, indicate that the original male was a true F_1 cross of $A \times C3H$. None of the progeny has yet shown any indication of the color changes that occurred in male No. 2129.



A HIMALAYAN-LIKE MOUSE

Figure 3

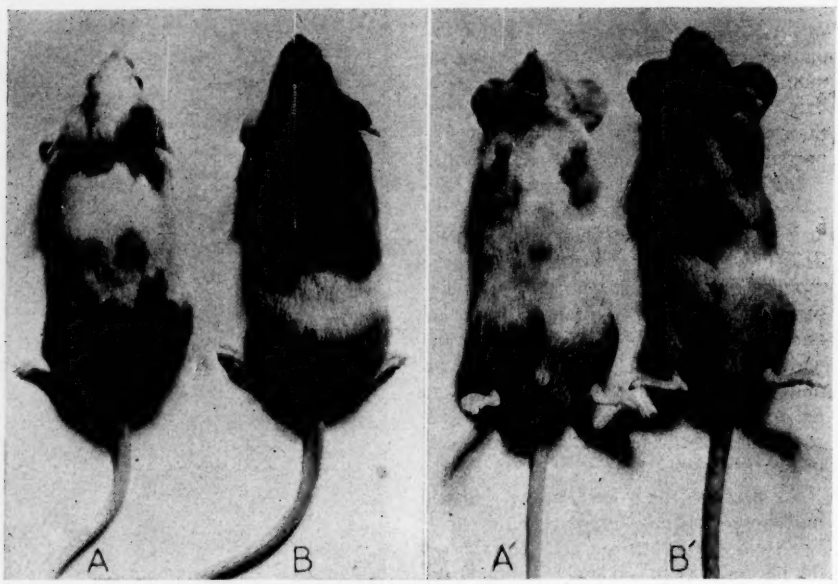
Mouse at twelve months of age, corresponds to Fig. 2*E* in the diagram. The distribution of pigment closely approaches that of the Himalayan rabbit and the Siamese cat. In these breeds the dark points are conditioned by the lower temperature of the extremities.

*This work has been aided by grants to the laboratory from the Commonwealth Fund, Anna Fuller Fund, International Cancer Research Foundation, Jane Coffin Childs Memorial Fund and the National Advisory Cancer Council. Thanks are extended to Dr. George W. Woolley of this Laboratory for his very kind and valuable assistance.

BELTED, A NEW SIXTH CHROMOSOME MUTATION IN THE MOUSE*

J. M. MURRAY and G. D. SNELL

University of Maine and Roscoe B. Jackson Memorial Laboratory



PIEBALD AND BELTED SPOTTING

Figure 4

A and *A'* show dorsal and ventral surfaces of "old-style" piebald mouse. The distribution of the white areas in this type of spotting is quite variable. The white face, characteristic of the strain from which this mouse comes, is absent in many other strains. In the presence of certain modifying genes piebald is not distinguishable with certainty from belted (*B* and *B'*). Belted is a recent mutant and has not been introduced into as many genetic backgrounds as piebald. Current observations suggest that the belted gene will prove to be less variable and less subject to the action of modifiers than piebald. Note that the ventral white area is larger than the dorsal in the piebald mouse, but that the reverse is true in the belted animal.

IN October, 1936, a male with a small, white, dorsal patch appeared in the University of Maine subline of the *dba* strain. This original male died before reaching maturity, but in subsequent matings of related animals the spotting reappeared and in due course a pure breeding spotted strain was established. Tests have shown this spotting to be inherited as a Mendelian recessive, distinct from piebald, and linked with the previously known char-

*This mutation was found by Dr. Murray at the University of Maine. Crosses which he completed demonstrated it to be a new recessive mutation distinct from piebald. At this point his tests were interrupted by his enlistment in the Intelligence Service of the United States Army Air Corps. Dr. Murray, therefore, very kindly turned the mutation over to me, and the linkage tests were carried out at this laboratory. The latter portion of the work has been aided by grants to the Roscoe B. Jackson Memorial Laboratory from the Commonwealth Fund, Anna Fuller Fund, International Cancer Research Foundation, Jane Coffin Memorial Fund, and National Advisory Cancer Council.—G. D. SNELL.

acters caracul and naked. It has been given the name "belted" (symbol *bt*).

A typical belted animal is shown in Figure 4*B* and *B'*. The area of dorsal white ranges from one per cent to twenty per cent of the total dorsal surface, and the ventral patch varies through about the same range. Contrary to the condition in piebald, the dorsal patch is larger than the ventral in the majority of animals, although the reverse condition is not uncommon (Table I). The patch is usually located back of the mid-point of the back, is usually broader than long, and may unite with the ventral patch on both sides to form a complete belt.

The data showing the Mendelian inheritance of the character are given in Table II. All ratios are close to the expected. Despite the fact that the area of white is often quite small we have found no proven cases of normal overlaps and if they occur at all they are certainly rare in the genetic backgrounds into which the mutation has so far been introduced. In the linkage crosses some animals appeared with ventral spots only. Genetic tests of two of these showed them to be heterozygous (Table III). A third animal homozygous for flexed tail and showing three per cent dorsal and eight per cent ventral white also was shown to be *Btbt*. The considerable spotting in this case is probably due to the effect of the flexed tail gene which not infrequently produces a ventral spot. Most *btbtff* animals obtained in the linkage crosses showed increased ventral spotting. One animal with one-half per cent dorsal and four per cent ventral white was shown to be *btbt*. On the basis of these results all F_2 and backcross animals with a ventral spot only have been classified as heterozygous, all animals with a dorsal spot (except for the one flexed tail animal mentioned above) as homozygous. This method of classification may have introduced an error which could have been eliminated by testing all doubtful animals, but the error is certainly small.

Crosses of belted with piebald, the previously known recessive spotting of the mouse, give unspotted F_1's, or F_1's with a small ventral spot such as not infrequently occurs in mice heterozygous for either of the two genes concerned.

Linkage tests have located the belted gene on the sixth chromosome with caracul and naked, the order being *bt Ca N*, and the crossover values 11.5% between *bt* and *Ca*, and 2.8% between *Ca* and *N* (Table IV). Curiously enough, the crossover values, contrary

Table I. Frequency distribution of spotting types among animals listed in Table IV.

No white	Ventral white but no dorsal white	More ventral white than dorsal white	Not more than 5% difference in dorsal and ventral white	More dorsal than ventral white	Dorsal white but no ventral white	Total	Not included
121	13	18	73	43	1	868	88
134		134					

Table II. Ratios given by different types of matings involving the bt gene

Mating		+	bt	Total
btbt x btbt	observed	0	27	27
	expected	0	27	27
Btbt x btbt	observed	144	152	296
	expected	148	148	296
Btbt x Btbt	observed	217	65	282
	expected	211.5	70.5	282

Table III. Tested animals of doubtful belted genotype

Number	Phenotype	White spotting: Dorsal	White spotting: Ventral	Belted genotype
9?182	bb	0	5	Btbt
♂1259	bbff	5	8	Btbt
9?287	sabbcd	0	1	Btbt
9?805	sabb	1½	4	btbt

Table IV. Linkage of belted with caracul and naked

Mating	bt+	+Ca	btCa	++				Crossover % btCa	
♀ bt+/+Ca x ♂btbt	27	37	2	5				11.5%	
♀btbt x ♂bt+/+Ca	12	6	2	0				10.0%	
	bt++	+CaN	btCaN	++N	btN	+Ca+	btCa	CaN
♀bt++/+CaN x ♂btbt	47	34	8	6	0	0	8.0%	0.0%
♀btbt x ♂bt+/+CaN	51	52	6	18	3	3	14.8%	4.7%

Table V. Negative linkage data and crossover percentages

Gene	Mating	++	+x	bt+	btx	No. of mice	Crossover per cent
f	F_2 repulsion	84	34	21	11	150	53.6±5.8
d	F_2 coupling	73	26	27	6	132	56.6±7.0
f	F_2 repulsion	61	20	21	8	110	56.7±6.8
va-2	F_2 repulsion	86	15	25	8	132	51.6±6.0
sh-2	F_2 repulsion	78	21	26	7	132	50.0±6.8
fv	BC coupling	30	22	55	22	109	47.7±4.8
a	BC coupling	63	54	53	65	235	48.5±3.3
b	BC coupling	48	50	43	38	173	53.7±3.8

to the usual condition, are higher in the male than in the female, in fact in the case of *Ca* and *N* all six crossovers occurred in the male. Cooper[1] obtained similar results in his original crosses with *Ca* and *N*. Adding his data to ours, there have been 12 crossovers in 392 backcross animals from heterozygous males, 0 crossovers in 158 backcross animals from heterozygous females. The difference is apparently significant (P = .043). It is to be hoped that when another sixth chromosome mutation is found the linkage tests will again include both *Ca* and *N* so that further data can be obtained.

The results of various negative linkage tests are given in Table V.

Summary

Belted (*bt*), a new recessive spotting mutation in the house mouse, is characterized by dorsal and ventral white areas, or sometimes by a white band encircling the body, the white areas usually being slightly posterior to the mid-trunk region. There is commonly more dorsal than ventral white. The character is linked with caracul (11.5% crossing over) and naked, the order of the genes being *bt-Ca-N*.

Literature Cited

1. Cooper, C. B. *Jour. Hered.* 30:212. 1939.

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DE-STERILIZATION

PERHAPS the most serious barrier to sterilization as a eugenic measure is its irreversibility. We must sympathize with the viewpoint of individuals who would be content with one or two children but who nevertheless hesitate to take a step which will make it impossible for them ever to have any more. What if the children they have should die? It would be a far greater tragedy if others could never take their places. Hesitation in the face of such a grim alternative is not hard to understand. Were it not so irrevocably "for keeps" many couples might find this method preferable to existing contraception.

Hence the growing number of cases in which male fertility has been restored years after sterilization have considerable eugenic interest, and may well be a very important factor in increasing the use of sterilization as a eugenic expedient. The most recent report of such a case comes from the Medical Corps of the Navy (*Jour. Amer. Med. Assoc.* 127:1119-1120). An enlisted man had been voluntarily sterilized in 1939, at which time he and his wife decided that they did not want any children. The war and the current baby-parade had changed their attitudes, and in 1944 "what he most wanted 'was to have the tubes put together again.'" The operation was performed by Lt. Commander Charles S. Cameron. Three months later many spermatozoa were present in the semen, but there is no report as yet of the overt fertility of the couple.

Dr. Cameron cites several other published instances wherein repair of the vas has resulted in restoration of fertility as long as seven years after the original operation. Hence there are good grounds for maintaining that in the male at least, sterilization by vasectomy is not an irrevocable step, and that if circumstances alter cases, what has been severed can be successfully reunited by a rather simple operation.—R. C.

MISTY DILUTION IN THE MOUSE*

GEORGE W. WOOLLEY

AN exceptionally light colored male mouse was found in the 25th generation of brother-sister inbreeding in the dilute brown (JAX dba, *ddbbaa*) strain of mice. This individual possessed a white tail tip and a unilateral rectangular-shaped white belly spot. White spotting was not characteristic of the parental stock.

It has been found that the dilution was due to a recessive mutation. The gene has been designated *m* (misty).[1] Evidence is here presented that misty is linked with brown and that white spotting is associated with the coat color dilution in certain combinations.

Linkage of Misty and Brown

Linkage of misty and brown was studied in a cross *MmBb* × *mmbb*. Six hundred and twenty-six mice were classified. Two hundred and eighty-four were misty-brown, 297 black, 27 brown and 18 misty-black. The results show misty to be 7.2 crossover units from brown.

The major part of the data were secured from a cross where the female was the heterozygous parent. However, 61 mice were from matings where the female was the homozygous parent. Of these 61, 23 were misty-brown, 33 black, 2 brown and 3 misty-black. The crossover percentage was 8.2 in this instance. Litter size was 4.4 in the latter group when colors were classified at the time the mice were between two and three weeks of age. Litter size for the group of 626 was 6.8.

White Spotting

White spotting has not been found in the inbred dilute brown strain of mice in which the mutation, misty, originated. However, the first mutant, a male, had a white tail tip and a unilateral white belly spot. It has been possible to maintain inbreeding and to observe the segregation of white spotting in *ddmmbbaa* mice as compared to that in *ddMmbbaa* sibs. There were no white tail tips or white belly spots on 64 *ddMmbbaa* mice thus classified. All but one of the 53 *ddmmbbaa* mice classified had white tail tips. Several had minute white tail tips. Two mice had white belly spots, the original male and a misty daughter produced by mating this male with his mother. Through several later generations white belly spot has not again appeared.

Record of the presence or absence of white tail tip was kept on 569 of the F_2 generation mice obtained in the linkage study. Data were used only where complete record had been made for the whole litter. The results are shown in Table I. One hundred per cent of the mice had white tail tips when *mm* was present and when *Mm* was present only 51-61 per cent of the mice had white tail tips.

A record of the presence or absence of white belly spot was made on the same group of 569 F_2 individuals from which white tail tip data were obtained. The results are shown in Table II. The frequency of white belly spots ranged from 70-71 per cent in *mm* individuals to two per cent in *Mm* mice.

It was found that in all cases where white belly spot occurred, whatever the genotype, white tail tip was also present. However, where white tail tip was present, white belly spot did not necessarily occur. Seventy-one to 100 per cent of the *mm* individuals with white tail tips had white belly spots, but four to zero

*This work has been aided by grants from the Commonwealth Fund, Anna Fuller Fund, International Cancer Research Foundation, Jane Coffin Childs Memorial Fund and the National Advisory Cancer Council.

per cent of the *Mm* mice with white tail tips had white belly spots. See Table III.

Discussion

Linkage of misty with brown constitutes the first gene linkage known with the brown locus,* although brown has been recorded as a mouse color for over a century and in recent years has been tested against many mouse genes.[2] Since *mm* tends to approach intense color and is therefore more difficult to identify than blue dilution (*dd*) or leaden (*ln ln*), it seems desirable that it be linked with a distinctive gene such as brown. However, with the two gene locations only 7.2 crossover units apart, misty may add little to the value of the brown locus itself in detecting other genes on this chromosome. With most of the 20 haploid mouse chromosomes now marked, a determined search for loose linkages with known gene locations will soon be in order.

It is not surprising that certain tendencies to white spotting are associated with misty coat color dilution. There are numerous examples among mouse genes of manifold effects conditioned by a single locus. Grey-lethal, for example, affects not only coat color but also the development of bones. It is of interest to consider the constellation of effects, flexed-tail, belly-spot and anemia, conditioned by a single locus. In this case both the tail abnormality and the belly spot often fail to manifest themselves in the homozygote, while the anemia behaves as a simple recessive character. The possibility exists that even further variation in the association between misty and white spotting may exist in various genetic backgrounds than was observed when misty was homozygous in the inbred dilute brown strain and in the segregating F_2 generation. An observation which was not brought out by the numerical data on white spotting was that the white tail tips and white belly spots were much larger in the F_2 generation mice than in the inbred dilute brown mice. Further study of misty may advance our knowledge of the basic processes of normal development and of gene action.

Summary

The coat color dilution factor, misty (*m*), has been found linked to brown with a crossover percentage of 7.2. Evidence is presented that misty is associated with white tail tip and white belly spot on certain genetic backgrounds.

Literature Cited

1. Woolley, George W. *Amer. Nat.* 75: 507-508. 1941.

2. Snell, G. D. (Editor) Biology of the Laboratory Mouse. Blakiston, Philadelphia. 1941.

Table I. Segregations of White Tail Tip in F_2 Generation Mice

Type	Number in each color class	Number with white tail tips	Percent with white tail tips
mb	258	258	100
MB	268	164	61
Mb	26	15	58
MB	17	17	100

Table II. Segregations of White Belly Spots in F_2 Generation Mice

Type	Total number in each class	Number with white belly spots	Percent with white belly spots
mb	258	182	70
MB	268	6	2
Mb	26	0	0
MB	17	12	71

Table III. Association of White Tail Tips and White Belly Spots in F_2 Generation Mice

Type	Number with white tail tips	Number with white belly spots	White belly spots with white tail tips	
			Number	Percent
mb	258	182	182	100
MB	164	6	6	4
Mb	15	0	0	0
MB	17	13	13	71

*Dr. G. D. Snell reported the linkage of an induced translocation causing semi-sterility with brown. *Genetics* 26:169. 1941.

A CHROMOSOME MAP OF THE MOUSE

Prepared by the STAFF OF THE ROSCOE B. JACKSON MEMORIAL LABORATORY

THE mouse has 20 pairs of chromosomes and up to the present time 10 of these have been mapped. On these 10, as shown in Figure 5, are 29 known loci, five of which have produced more than one mutant gene (multiple alleles). Several genes are indicated by a symbol but are not illustrated. These are: *o* = oligodactylie, *kr* = kreisler, *we* = wellhaarigkeit, *an* = anemia. Because these four genes have been tested against only one locus on the chromosome on which they are located, their actual position is still uncertain. Besides the genes belonging to identified linkage groups, there are 28 mutant genes as yet unlocated. The following figures are reproduced by the courtesy of the publishers: rodless retina, Keeler, 1924, *Proc. Nat. Acad. Sci.;* silver, Keeler, The Laboratory Mouse, 1931; hairless & rhino, Howard, 1940, *J. Hered.;* naked, Snell, 1931, *Genetics;* waved-2, Keeler, 1935, *J. Hered.*

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Contributions in Mouse Genetics

(Continued from contents page)

normal, are being studied as are the broader non-Mendelian types of parental influence. Mice, rats, hamsters, rabbits, guinea pigs and dogs are being selectively bred and studied.

The contributions which make up this issue of the JOURNAL are by-products of the main cancer research program. Over a third of a million mice are born each year in the laboratory's breeding pens. Under the watchful eyes of the staff members, a number of mutations have been observed. A few of the more striking or more useful are reported in this issue.

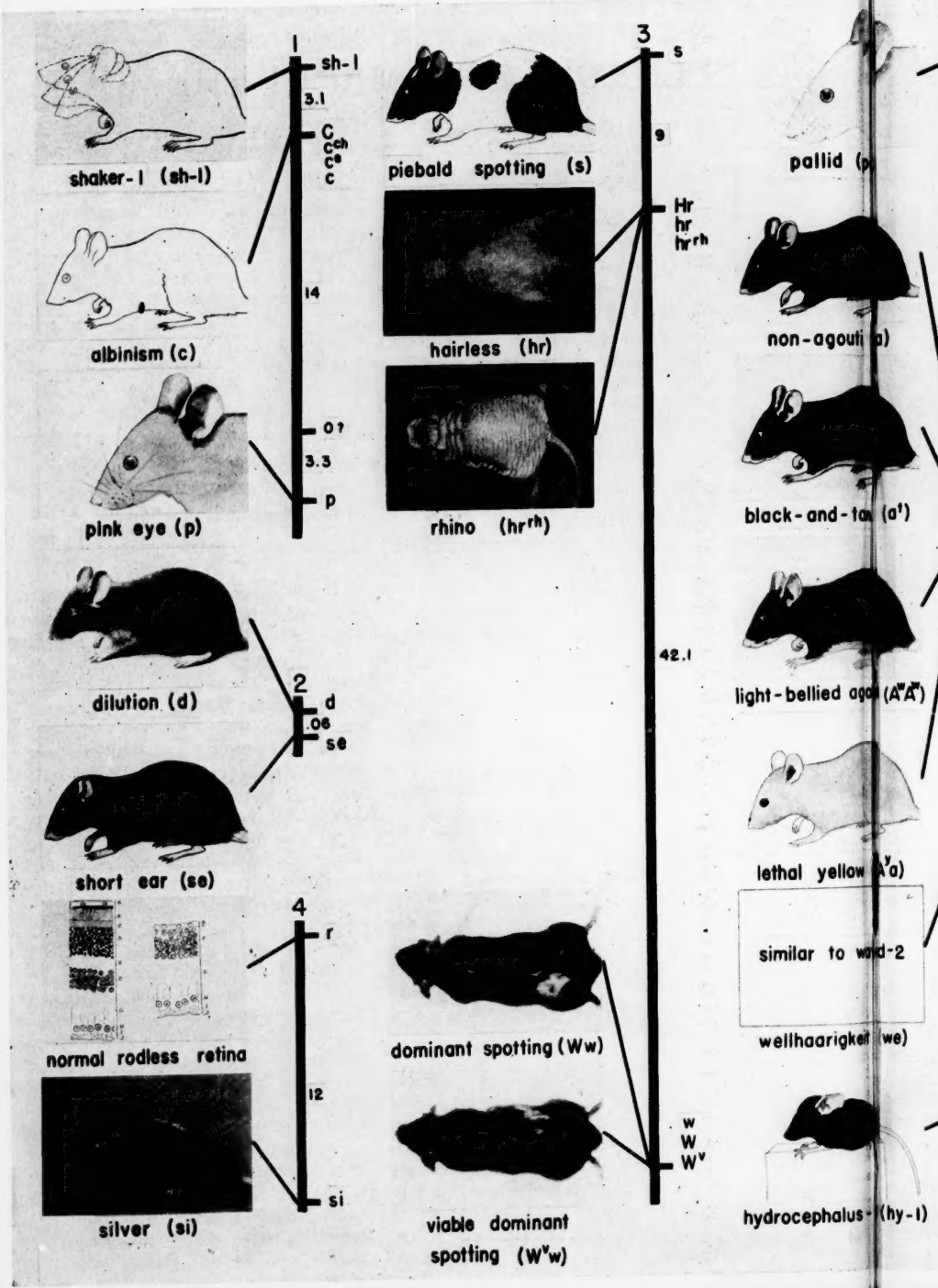
None of the abnormalities here described is directly concerned with cancer. Yet all of them have a bearing on the problem in the sense that they add to the knowledge of mouse genetics and physiology. As their positions on the chromosomes are determined through linkage studies, some will be valuable as the markers which eventually will lead to localization on specific chromosomes of some of the genes directly involved in cancer susceptibility. Hence they do have a very real importance in the basic program of the laboratory as well as in the field of mammalian genetics.

Probably the most significant discovery which has come from the Jackson Laboratory program is the establishment of non-chromosomal factors in the inheritance of cancer. This is most strikingly demonstrated in the so-called "milk influence," whereby a newborn female mouse of a non-cancer strain, if nursed by a cancer strain foster mother, will display her foster mother's cancer susceptibility. In the reciprocal experiment the foster daughter follows the foster mother's phenotype with respect to cancer immunity. In connection with these experiments many ingenious techniques have been developed, such as large-scale transplantation of fertilized ova from one female to another.

The Roscoe B. Jackson Memorial Laboratory was incorporated under the laws of Maine in 1929 as a charitable, non-profit organization. Its purposes as stated in the Articles of Incorporation are as follows:

"For literary, scientific, charitable, educational and benevolent purposes—the corporation to be entirely devoted to charity and the welfare of mankind."

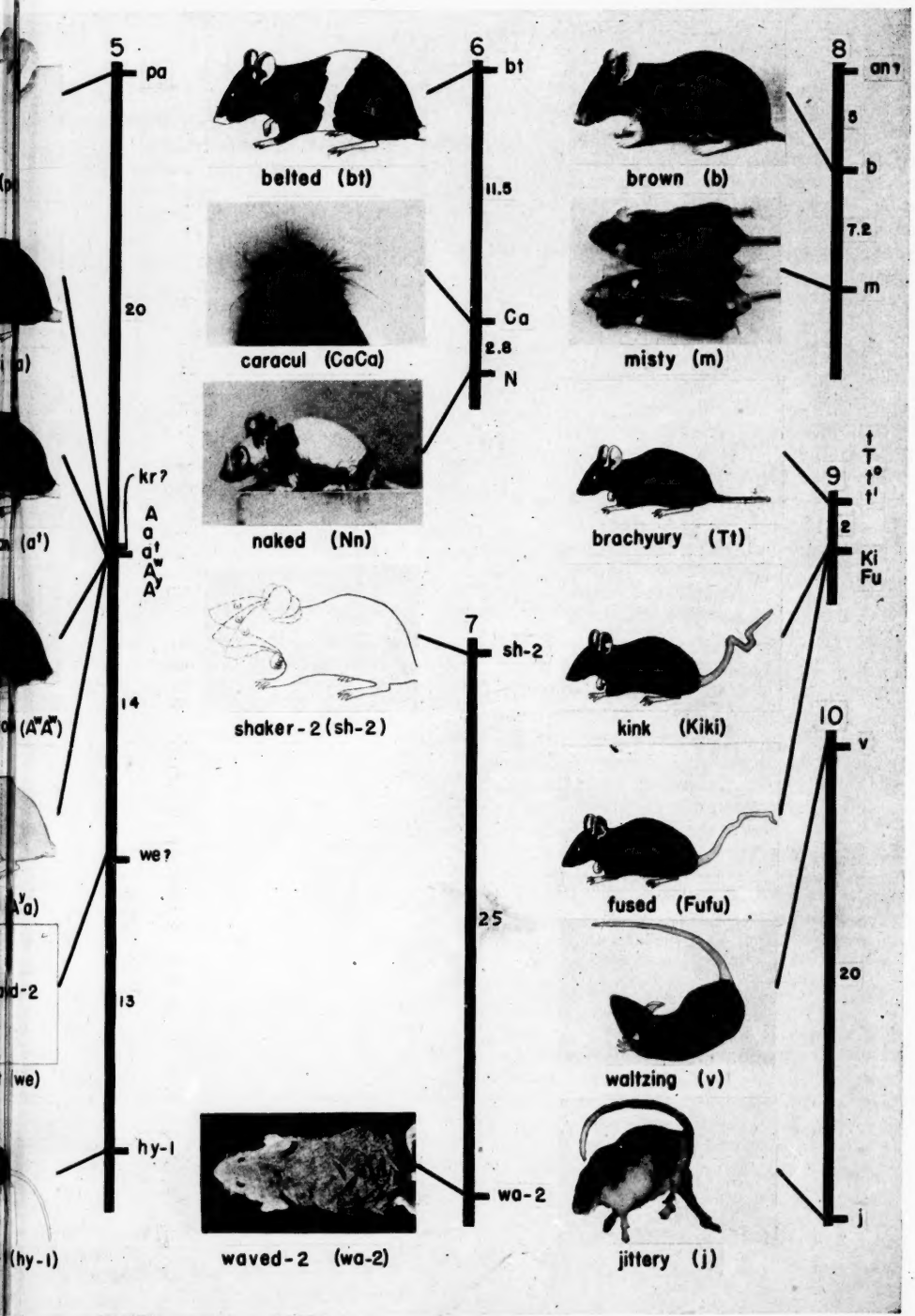
The land on which the main laboratory is situated lies in the town of Bar Harbor on Mount Desert Island some



A CHROMOSOME MAP OF

Fig. 5

Of the 57 known genes in the mouse, 29 have been found to be linked. Seven sex-linked genes are known in the mouse.



P OF THE MOUSE

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o be linked on ten of the twenty pairs of chromosomes. No

eighty miles by water from the Canadian border at the northwest corner of the United States.

The Laboratory was founded by the generosity of George Buckman Dorr, Edsel Bryant Ford, Louise Webber Jackson and Richard Hudson Webber who gave the land and original building. In 1939 a substantial addition to the building was made possible by a gift from the Rockefeller Foundation. In 1941 Mr. and Mrs. William Pierson Hamilton gave to the laboratory a large farm with several modern buildings. This, with an adjoining tract given in 1942 by Mr. Oscar Webber, is known as the Hamilton Station. In 1943 additional property and buildings known as "Aldersea," the estate of the late Miss Mary Coles of Philadelphia, was given to the Laboratory by her heirs, Messrs. Edward C., George A., James M. and Oliver W. Robbins. This property is located between the main laboratory and the town of Bar Harbor.

The Laboratory has no endowment and is dependent upon grants, donations, and legacies as well as upon funds derived from the sale of surplus animals.

The legally designated officers of the Laboratory are a Board of Directors, President, Vice-President, Treasurer and Clerk. There are also other officers as shown below.

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The Members of the Laboratory who represent persons of distinction interested in the development of the institution include, among others, the following: J. J. Bittner, Ph.D.; H. S. Boardman, D.C.E, LL.D.; G. H. A. Clowes, Ph.D.; R. C. Cook; G. P. Dike; Hon. H. Hildreth, Governor of Maine; J. F. Johnson, M.D.; M. R. Lewis, Ph.D.; W. H. Lewis, M.D.; W. S. Murray, Sc.D.; J. H. Ripley, M.C.E.; J. M. Robbins; A. F. Shull, Ph.D.; E. G. Stillman, M.D.; L. C. Strong, Sc.D.; R. R. Spencer, M.D.; and L. J. Cole, Ph.D.

The full time staff of the Laboratory engaged in independent investigation is composed of:

Arthur M. Cloudman, Research Associate and Pathologist, B.S., M.S., Maine; Ph.D., Michigan.
Elizabeth A. Fekete, Research Associate, B.A. Teacher's College, Budapest; A.M., Michigan.
Katharine P. Hummel, Research Associate, A.B., Carleton College; M.S., Minnesota; Ph.D., Cornell.
Margaret A. Kelsall, Research Fellow, A.B., Ph.D., Colorado.
Clarence C. Little, Research Associate, A.B., M.S., Sc.D., Harvard; LL.D., New Hampshire, New Mexico, Albion, Colby; Litt.D., Maine.
William L. Russell, Research Associate, B.A., Oxford; Ph.D., Chicago.
J. P. Scott, Research Associate, A.B., Wyoming, Oxford; Ph.D., Chicago.
George D. Snell, Research Associate, B.S., Dartmouth; M.S., Sc.D., Harvard.
Emelia M. Vicari, Research Fellow, A.B., A.M., Smith; Ph.D., Cornell.
George W. Woolley, Research Associate, B.S., Iowa; M.S., Ph.D., Wisconsin.

Part Time Investigator

Elizabeth S. Russell, Research Fellow, A.B., Michigan; Ph.D. Chicago.

Among the Foundations aiding the work with grants-in-aid are the following: The Jane Coffin Childs Memorial Fund for Medical Research, The Commonwealth Fund, the Ford Foundation, the Anna Fuller Fund, the International Cancer Research Foundation, the National Advisory Cancer Council and the Rockefeller Foundation.

THE DETECTION OF MUTATIONS

Relative Efficiency of Various Systems of Brother-Sister Inbreeding of Mice

G. D. SNELL

THE production of mice by repeated brother × sister matings is now standard practice in maintaining many stocks in many laboratories. Because inbreeding is more apt than random breeding to bring recessive mutations to light, the practice has undoubtedly favored the discovery of new mutations in mice. Within the inbred stocks themselves another factor, the number of sublines maintained, affects the chances of detecting mutations. It is the purpose of this paper to present the results of some calculations showing just how important this factor is.*

The five methods of breeding selected for consideration are based on those used at the Jackson Laboratory. Since methods used in different laboratories do not differ greatly, the results in their essentials should be generally applicable.

The calculations for each system of breeding are expressed in two ways: (1) the probability that a recessive mutation occurring in any breeding animal will appear in the homozygous condition in one or more animals of a later generation; and (2) the number of mutations discovered per pen per generation, expressed in terms of the mutation rate, r (Table I). The second figure is a direct measure of the efficiency of the system for the detection of mutations. The calculations are carried out so that the third decimal place should be accurate to within ± 2. In all cases it is assumed that only brother-sister matings are used, and that the number of breeding pens remains constant in successive generations. It is also assumed that from each breeding female 17 young are raised to weaning and checked for mutations. This figure is not completely arbitrary, but was found to be the average for a number of females from one stock. If we assume that each female raised a somewhat larger number of young, this would change the results only slightly.

System 1

The system most commonly used at the Jackson Laboratory is to make up pens with several females, usually four, and one male, and when females become pregnant to isolate them in separate "preg" pens. When the stock is a fairly fertile one, it is found advisable to allow three "preg" pens to each two breeding pens. Usually no particular effort is made either to maintain or to eliminate minor sublines (certain major sublines of some stocks are especially maintained and appropriately designated). There is a tendency, however, for sublines to be eliminated due to the fact that by chance only a fraction, perhaps one fourth to three fourths, of the breeding pens in one generation will supply breeding pens for the next generation. Some of the sublines that do supply breeding pens provide two or more.

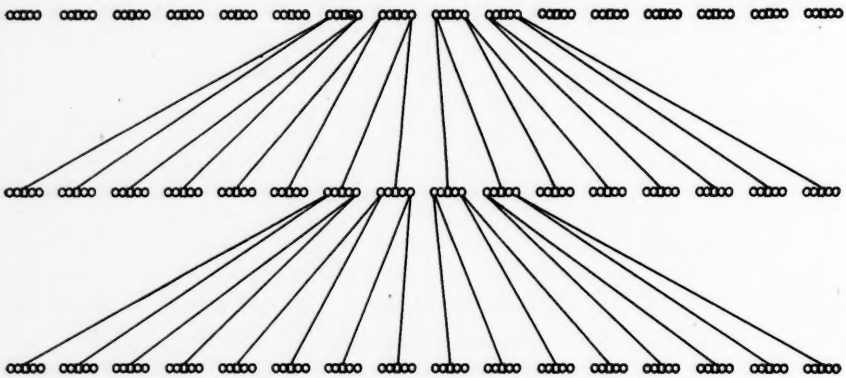
The particular assumptions made in calculating the chance of detection of mutations under this system of breeding are indicated in Figure 6. It will be seen that a rather high degree of elimination of sublines is presupposed.

This system is the least efficient of

*I am much indebted to Prof. Sewall Wright for reading the manuscript of this paper. He has most kindly developed a general formula for cases 2, 4, and 5, as follows:

$$X = \frac{2}{n+1} \times \frac{2 \times 2^{n-1} - 1}{3 \times 2^{n-1} - 1}$$

where X = the chance that a recessive mutation occurring in any breeding animal is detected, and n = the number of breeding females per pen. This formula assumes that enough young are raised so that all detectable recessives appear in the progeny of matings of type *Aa* by *Aa*. This differs slightly from the assumption that I have made, but the differences in the results are negligible.



SYSTEM 1—SUBLINES RAPIDLY ELIMINATED

Figure 6

Each breeding pen contains five mice—four sisters and a brother. As the females become pregnant they are isolated in separate "preg" pens. In calculating effectiveness of the five systems used it is assumed that 17 young are raised to weaning from each breeding female. This system is inefficient for the detection of mutations, the number of recessive mutations discovered per pen per generation being only 0.25 r (Table I), where r is the mutation rate, as compared with 1.00 r for system 4.

all those considered for the detection of mutations. (Table I).

System 2

This system, illustrated in Figure 8*A*, is the same as system 1 except that the maximum number of sublines is maintained, each breeding being used to produce one and only one breeding pen in the following generation. In actual practice this ideal could only be approximated because of sterility and accidental deaths. System 2 is slightly more than twice as efficient with respect to mutation detection as system 1.

System 3

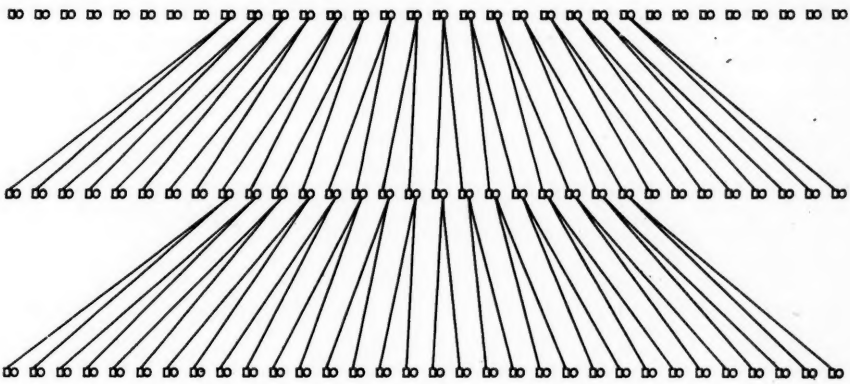
Another system used at the Jackson Laboratory, and particularly recommended by Grűneberg,[1] is the "1 and 1" system in which each pen contains one female and one male, and pregnant females are not isolated. This, like the "4 and 1" system, can be combined with any degree of subline elimination or retention. In the calculations for system 3, a 50 per cent elimination in each generation is assumed (Figure 7). Despite the high subline elimination, this system is slightly more efficient for the detection of mutations than system 2 because more breeding pens and hence more sublines can be maintained in a given space.

System 4

This is the same as system 3 except that the maximum possible number of sublines is retained (Figure 8*B*). It is approximately four times as efficient for the detection of recessive mutations as system 1, and 60 per cent more efficient than system 3.

System 5

In a few cases where large numbers of mice are desired it is found useful to use two females and a male in a pen without isolating pregnant females in separate pens. This has the disadvantage that it may result in overcrowding and that it will sometimes lead to the accidental use of half-brother × sister instead of brother × sister mating. Combined with maximum subline retention (Figure 8*C*), it is 20 per cent more efficient for mutation detection than system 4, but this is probably offset by its disadvantages.



SYSTEM 3—SUBLINES RAPIDLY ELIMINATED

Figure 7

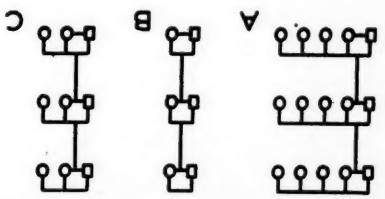
Each breeding pen contains a single brother-sister pair. "Pregs" are not isolated. Assuming that 17 young are raised to weaning from each breeding female, the number of recessive mutations discovered per pen per generation is 0.62 *r*. System 3 is slightly more efficient than system 2.

Value of Sublines in the Maintenance of Stocks

The maximum retention of sublines is valuable from the point of view of mutation detection. Is it valuable or detrimental from the point of view of maintaining a genetically vigorous inbred stock?

Before attempting to answer this question, it should be emphasized that for an experiment where a high degree of genetic uniformity is important, only closely related sublines should be used. This may mean selecting one subline and expanding it to provide the necessary animals. In many cases, however, subline differences, being much less than strain differences, may be unimportant.

Although it results in the accumulation of genetic variability (in fact largely because of this), the retention of sublines is a help in maintaining a vigorous stock. There is much theoretical and some experimental evidence to indicate that slightly deleterious mutations are continually occurring in inbred lines. Such mutations might, for example, cause eye defects, or a low percentage of sterile males. Where maximum subline elimination is practiced, it will happen occasionally as a matter of chance that retained animals will trace back to a single pair homozygous for a deleterious but at first unsuspected mu-



SYSTEMS 2, 4 AND 5—ALL SUBLINES RETAINED

Figure 8

A—System 2, four females and one male per home pen, "pregs" isolated in separate pens, 17 young raised to weaning by each breeding female. This is about twice as efficient for the detection of recessive mutations as system 1, the number of recessive mutations detected per pen per generation being 0.52 *r* (Table 1).

B—System 4, differs from 2 in that there is only one female per pen and "pregs" are not isolated. The number of mutations detected per pen per generation is 1.00 *r*.

C—System 5, differs from 4 in that there are two females per pen. Mathematically this is better than system 4, the number of mutations detected per pen per generation being 1.20 *r*, but in practice it would often be less satisfactory.

tation. Once this happens, the more desirable lost allele can never be recovered in this particular stock. On the other hand, if numerous sublines are retained this difficulty will rarely arise. If one subline becomes suspect as the carrier of a new defect because of any form of reduced vitality exhibited through successive generations, this subline can be dropped and a more vigorous subline expanded to replace it.

It is pertinent in this connection to quote the following from D. F. Jones.[2]

> For the practical breeder the maintenance of homozygous inbred lines is a matter of serious concern. The possibility of continued production of degenerative loci must be guarded against by progeny testing or valuable lines will be lost or reduced to such a low level of vigor that they can be used only with difficulty. For theoretical genetics it is worth while to note that there is the possibility of continued degeneration. This takes place in crossbred as well as inbred families and has nothing to do with inbreeding but is more apparent after consanguineous mating and more quickly eliminated. The prevention of chromosome degeneration and the elimination of defective loci after they are formed, in organisms not exposed to rigorous natural selection, is one of the major problems of the future.

Summary and Conclusion

Five systems of brother × sister inbreeding are compared with respect to their efficiency for the detection of recessive mutations. The systems differ in the number of breeding females per male, in whether or not pregnant females are isolated, and in the degree to which sublines are retained. The least efficient system is one in which there are four females per male, pregnant females are isolated, and sublines are rapidly eliminated. As compared with this system, the number of recessive mutations discovered per pen per generation can be increased four times if there is one female per male, "pregs" are not isolated, and all sublines are retained. In practice, the number of recessive mutations discovered should be increased materially, perhaps doubled, by the more widespread adoption of methods of breeding approximating the latter system. Reasons are given also for preferring this system to maintain inbred stocks with a minimum of genetic deterioration.

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Table I. Comparison of five systems of brother x sister inbreeding.

System	No. of females per home pen	Minimum No. of pens		No. of generations after which all mice in a section of 32 or 40 pens trace to 1 pair	Chance mutation is found*	Mutations discovered per pen per generation†
		home	preg			
1	4	16	24	4	.125	0.25 r
2	4	2	3	∞	.261	0.52 r
3	1	32	0	6	.308	0.62 r
4	1	1	0	∞	.499	1.00 r
5	2	1	0	∞	.399	1.20 r

*More precisely, the probability that a recessive mutation occurring in any breeding animal will appear in the homozygous condition in one or more young of a later generation.

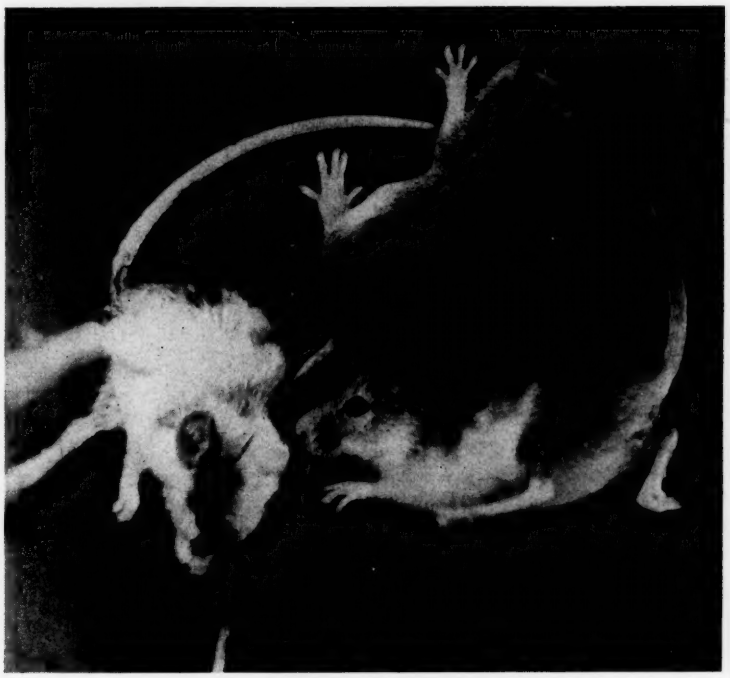
†Where r = the mutation rate for recessive genes for all loci combined. Of course many, probably most, mutations, even those producing pronounced (internal and/or lethal) effects, are overlooked by ordinary methods of observation. Therefore, strictly, r is the rate of occurrence of mutations detectable by the methods of observation used.

LINKAGE OF JITTERY AND WALTZING

In the Mouse*

G. D. SNELL

Roscoe B. Jackson Memorial Laboratory



JITTERY MICE

Figure 9

Three homozygous jittery mice about three weeks old. Note inability to stand upright and characteristic tetany (tremor) in the right hind leg of the smallest mouse.

JITTERY is a new recessive juvenile lethal mutation in the mouse characterized by muscular incoordination and tetany.[1]† Affected animals are first distinguishable from their normal littermates at about 12 days of age by the fact that in running they lean to right or left. The character, thereafter, becomes progressively more extreme. At about 14 days the mice, when attempting to walk, fall on one side whereafter they experience considerable difficulty in righting themselves. In another day or two tetany appears, involving most conspicuously the front legs which beat rapidly up and down when the mouse is excited. The animals fall behind their normal sibs in weight, their

*This work has been aided by grants to the Roscoe B. Jackson Memorial Laboratory from the Comonwealth Fund, Anna Fuller Fund, International Cancer Research Foundation, Jane Coffin Childs Memorial Fund, and National Advisory Cancer Council.

†Dr. DeOme has kindly allowed me to read his manuscripts and to draw on it for the description of jittery given herewith. I am also very much indebted to Drs. DeOme and W. E. Castle for forwarding the mutation to this laboratory.

coats become rough, and death ensues at about 32 days of age (Figure 9).

To test for linkage of jittery with other known genes, heterozygous mice were crossed to animals of the following stocks.

CA stock	*CaCaFufuWw*
P stock	*aabbdse/dsepprr*
V stock	*aalnlnsstvwa-lwa-l*

F_1's were tested to determine if they carried jittery, then either backcrossed to jittery heterozygotes (CA F_1's) or mated *inter se* to produce an F_2 (P F_1's and V F_1's). The results are summarized in Table I.

Because the initial results suggested linkages with both *W* and *v*, additional tests were made involving both these loci. Crosses with the *W* locus (both *W* and W^v were used) failed to give further indication of linkage. For the tests with *v*, the cross used was $j+/+v \times ++/++$. This cross eliminates the possibility of a disturbance of the ratio through low viability of the *jjvv* genotype. Backcross animals were raised and tested genetically for the presence of *j* and *v*. In testing for *j*, ten animals without the appearance of the homozygous recessive were taken as proof that the animal being tested was *JJ*. In testing for *v*, since homozygous waltzers could be used as testers, five non-waltzing mice were regarded as proof that the mouse under test was *VV*. Actually, the numbers usually considerably exceeded the minimum limits set, particularly in the case of mice classified as *JJVV*, where the minimum numbers of mice for tests were 14 and 6 respectively.

Where the F_1 female was heterozygous, four of ten backcross mice were crossovers, where the F_1 male was heterozygous, five of 49 backcross mice were crossovers. The combined data show 15.3% crossing over. Because the method of testing employed may have resulted in one or more mice of the genotype *JjVv* being classified as *JJVv* or *JjVV*, the true crossover value is perhaps somewhat higher than this. The crossover percent calculated for the 125 F_2 animals is 26.2 ± 8.2.

Tests for linkage of *W* and *v* have never been made (Grüneberg[3]). The data here reported partly fill in this gap in that they prove that *v* and *W* at least cannot be very closely linked. The evidence for absence of linkage between *j* and *r* is valuable as a confirmation of Keeler's data[4] showing absence of linkage of *v* and *r*, since these latter consist of only a very limited number of F_2 mice.

Summary

Jittery is linked with waltzing. The two genes showed $26.2 \pm 8.2\%$ crossing over in an F_2, $15.3 \pm 6.5\%$ crossing over in a backcross.

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Table I. Linkage data and crossover percentages

Gene	Mating*	++	g+	+j	jj	No. of mice	Crossover per cent
a	F2 repulsion	41	14	12	3	70	15.6 ± 8.9
a	PBC repulsion	89	111	31	34	265	43.5 ± 5.3
Ca	PBC coupling	25	21	6	8	58	56.7 ± 11.3
Ca	PBC repulsion	47	47	19	13	126	55.6 ± 7.7
dse	F2 repulsion	214	41	59	21	335	>57.3
Fu†	PBC repulsion	46	22	13	9	90	43.2 ± 9.1
In	F2 repulsion	71	13	31	10	125	>57.3
j	F2 repulsion	191	64	58	22	335	51.7 ± 4.0
r	F2 repulsion	45	14	18	4	81	45.3 ± 8.7
s	F2 repulsion	67	17	31	10	125	53.4 ± 6.4
v	F2 repulsion	64	20	39	2	125	26.2 ± 8.2
v	PBC repulsion	7	24	26	2	59	15.3 ± 6.5
v	PBC coupling	21	41	12	9	83	32.2 ± 9.0
v	PBC repulsion	45	39	15	18	117	45.2 ± 8.0
W	PBC coupling	114	147	40	42	343	44.4 ± 4.7
wa-l	F2 repulsion	64	20	30	11	125	52.9 ± 6.5

*PBC (partial backcross) indicates a cross of the type $(a+)/(+j) \times (a+)/(aj)$. Coupling is used to mean that the two recessive factors entered the cross together, irrespective of whether or not they are both mutant genes, or one a mutant and the other a type gene. The backcross (BC) involving *v* and *j* was a cross of an F_1 double heterozygote to type; the presence or absence of waltzing and jitters in the backcross animals was determined by a genetic test.

†Because Dunn & Caspari (1942) have shown fused to be at a locus separate from brachyury (*T*), we have followed them in symbolizing it *Fu* instead of *Tf*.

PIROUETTING MICE*

GEORGE W. WOOLLEY AND MARGARET M. DICKIE
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BEHAVIOR patterns are inherited as Mendelian characters in the mouse. Among these may be mentioned those designated Japanese waltzer, shaker-1, shaker-2, jerker, shaker-short, jittery,[1] fidget[2] and Bochum waltzer. The individuals have usually been identified by peculiar head and body movements, characteristics often found associated with other peculiarities such as inability to react to sound. Much of the literature concerning such mutants has recently been reviewed.[3] This report concerns a mouse which in several respects seemed to belong in the above series.

The purpose of this investigation has been to determine if the character termed pirouette is a new mutant in the mouse, and if so to ascertain its method of inheritance. Another purpose has been to so describe the character that some idea of its usefulness for further studies, genetic, physiological, and anatomical, might be secured.

Origin

In 1943 two female mice which whirled in a manner similar to waltzing mice were observed in a litter of "low tumor" strain C3H mice (*Mus musculus*). The low tumor strain had been produced by foster nursing young of JAX strain C3H mice on JAX strain C57 black. This "low tumor" strain had been observed for three or four generations and used in experimental work without any other mice with peculiar behavior characteristics having been observed. Mice with this whirling or spinning characteristic and tracing to the above origin are in this report termed pirouette mice.

Genetics

Breeding data secured from matings of pirouette with pirouette and with normal mice are summarized in Table I. Animals were classified on the basis of whether or not the whirling and spinning behavior was present. Mice raised to weaning age were classified.

Pirouette × pirouette produced 40 mice. These were all uniformly pirouette. Since there was no tendency to normal overlaps the character seemed to be an effective one.

Pirouette × normal produced 32 mice. These were all normal. The evidence is that pirouette is completely recessive to normal. Additional evidence is presented below, where pirouette was crossed to mice of strains possessing mimic behavior characters, closely resembling pirouette.

Pirouette backcrossed to mice secured from mating pirouette with normal, resulted in 59 individuals. Twenty-nine per cent of these were pirouette. This is a marked departure from a 1:1 ratio; probably the result of litter depletion which was heavy through part of the series. The 59 mice were produced in 12 litters.

Heterozygous pirouette mice mated *inter se* produced 141 offspring. Twenty-eight per cent of these were pirouette which approximates the 3:1 ratio expected if pirouette is due to a recessive Mendelian character.

It is interpreted that pirouette is due to a unit recessive mutation and this is designated by the symbol *pi*.

Crosses with other Mutants

A summary of the results of crossing pirouette with several strains possessing characters of circus or of choreic nature are presented in Table II. It was found that F_1 generation mice were all normal in crosses between *pipi* and the follow-

*This work has been aided by grants from the Commonwealth Fund, Anna Fuller Fund, International Cancer Research Foundation, Jane Coffin Childs Memorial Fund and the National Advisory Cancer Council.

PIROUETTE MOUSE

Figure 10

Pirouette mouse 4½ months old, in characteristic position in performing a clockwise spin. The right forefoot is placed to the rear to act as a pivot.

ing: *sh-1 sh-1, sh-2 sh-2, vv, dervish,*[4] and *je je.** From a review of the literature it was interpreted that the above characters were the most similar to pirouette that have been described. No fidget mice (*fi fi*) were available for crossing, but this character may apparently be differentiated on the basis of any one of a number of different characteristics. Thus in fidget mice the circling is not as marked as is pirouette, nor do the mice become deaf until a later age (three to four months); the slow rate of growth for the first few weeks typical of fidget is not found in pirouette. The Bochum waltzers (*bo bo*) are different from pirouette in that they are able to hear in an apparently normal manner. The onset of circling in the mouse described by MacDowell appeared late in life and was interpreted as being due to the presence of two genes. Shaker-short mice (*stst*) are differentiated in that shortening or absence of the tail is combined with circus movements, lack of muscular coordination and deafness.

Description

Young *pipi* mice start peculiar behavior motions early in life. When disturbed and taken from the nest after about the tenth day the mice tend to turn sharply and to back rather than progress forward.

Probably the most characteristic peculiar movement of mature *pipi* mice is whirling rapidly in circles of small diameter; which suggested the name pirouette. Although the mice whirl too rapidly for detailed observation, photographs were taken of the mice in action and some details could be observed Figures 10 and 11). The mouse swings

**sh-1 sh-1, sh-2 sh-2, vv* and *jeje* mice were secured from Dr. George D. Snell of this laboratory and thanks are extended to him for these.

BABIES PIROUETTE TOO

Figure 11

This mouse is only 14 days old, and already the habit of spinning in small circles is well established. Before the whirling behavior begins at about ten days of age the pirouette mice can be identified by peculiar crab-like movements when they move about.

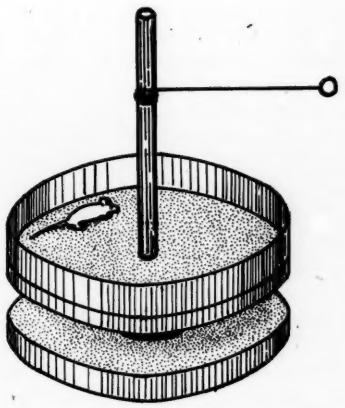
its head sharply to one side. places the inner forefoot back toward the rear foot, toes turned out, and seems to place the opposite forefoot in such a position that it aids in pushing the mouse into a small diameter rotation. The mice whirl incessently for long periods of time.

Other characteristic movements include occasional running in circles, the diameter of which is the same as the width of the mouse box in which they were observed (15 cm.) and figure eight movements limited by the size of the floor of the cage (15 cm. x 30 cm.).

One of the characteristic movements of *vv* mice in which the head is moved in a vertical manner and the nose maintained high momentarily, as if sniffing, is assumed by *pipi* mice from time to time but this behavior is not as pronounced in these mice as in the *vv* mice we have observed.

Pirouette mice seem to have no pronounced preference for right or left turning, the same mouse may whirl first in one direction and then in the opposite direction. Exclusive turning in one direction has not been observed.

Males and females appear to be equally active.



SOME MICE DON'T GET DIZZY

Figure 12

Cyclostat used in testing mice for rotational dizziness. The speed is determined by the revolutions of cord unwound in a given length of time. See the text for further description.

Pirouette mice observed after rotation in a cyclostat failed to give evidence of rotational dizziness. A cyclostat was made by mounting a circular, cloth covered, walled platform 12 inches in diameter on a bicycle wheel ball bearing (Figure 12). For a test run the mouse was placed near the edge of the platform and rotated one minute at 250 r.p.m. Three runs constituted a test; the result of the majority of the runs was taken as the reaction. Four other "uncoordinated" types, *sh-1 sh-1, sh-2 sh-2, vv,* and *je je* also failed to show the symptoms of rotational dizziness which normal mice exhibited. Cyclostat studies with mice have been described by Yerkes.[5]

Mice of the constitution *pipi* were tested for auditory response at weaning age (21 to 30 days). Sound was produced by sucking through closely pressed lips, by clicking water bottles and by quickly shutting a pair of hand shears of the type used for cutting metal. The mice failed to give evidence of reaction to sound. An interesting observation was that the cage could frequently be moved on the shelf and opened without *pipi* mice awakening. To mice outside the laboratory this failure of auditory

response might conceivably lead to fatal results. This deficiency, in addition to the obvious disadvantages of compulsive circling justifies the conclusion that pirouette would be a harmful character under natural conditions. *Pipi* mice responded to sound in an apparently normal manner as did mice of the constitution: *Pipi Vv, Pipi Dv dv, Pipi Sh-1 sh-1, Pipi Sh-2 sh-2,* and *Pipi Je je.*

Pirouette mice were unable to swim on the surface of water or to swim with coordination. This was also true for mice of the constitution *sh-1 sh-1, je je* and *sh-2 sh-2.* The literature carries reports that *fi fi* and *vv* mice are also unable to swim.

Discussion

Mice of the constitution *pipi* are easily distinguished from those which are *Pipi* and *PiPi.* The classification may be made on the basis of presence or absence of circus movements. Classification is also possible at a relatively early age, that is before the young mice leave the mother's nest by means of their peculiar "crab-like" movements when placed on a flat surface for a few moments. It would seem that the gene *pi* would be a good one upon which to base further studies, genetic, anatomical, physiological and psychological.

Summary

A character in the house mouse causing pronounced derangement of behavior is described. The character is in some ways comparable to that exhibited by mice homozygous for *v, sh-1, sh-2, fi, dv* and *je.*

Evidence is presented that the character is due to a unit recessive mutation.

A suggested name for the character is pirouette with the symbol *pi.*

Breeding tests show the gene *pi* is not identical to *je, sh-1, sh-2, v* or *dervish.*

Rotation of *pipi* mice on a cyclostat failed to produce symptoms of rotational dizziness.

Different methods of producing sound failed to elicit evidence of sound response in *pipi* mice.

pipi, je je, sh-1 sh-1 and *sh-2 sh-2* mice were tested and found to be unable to swim with coordination or on the surface of water.

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Table 1. Segregation of Pirouette

Mating	Pirouette	Non-pirouette	Total	Percentage pirouette
pipi × pipi	48	0	48	100
pipi × PiPi	0	32	32	0
Pipi × pipi	17	42	59	29
Pipi × Pipi	39	102	141	28

Table 2. Summary of results of crossing pirouette with other mutant stocks (circus and choreic movements)

Mating	Pirouette	Other mutant	Normal	Total	Percentage normal
pipi × jeje	0	0	14	14	100
pipi × sh-1 sh-1	0	0	12	12	100
pipi × sh-2 sh-2	0	0	9	9	100
pipi × dervish	0	0	11	11	100
pipi × vv	0	0	5	5	100

ABNORMALITIES OF THE MAMMAE IN THE HOUSE MOUSE*

C. C. Little and Helen McDonald

THE present communication records the incidence of abnormal number, degree of development and distribution of mammae in a number of inbred strains of *Mus musculus* and their hybrids. It considers these facts in terms of genetic influences and of their possible utilization for genetic studies.

The literature on mammary abnormalities in rodents is not very extensive. It is confined to statements of the incidence of such abnormalities with little if any attempt at tabulation or analysis.

Svihla[1] reported on the number of mammae in 213 females of two species of muskrat (*Ondatra zibethics* and *O. rivalicia*). The normal number is eight in 177 individuals; 22 had nine mammae and three had 10. This represents 16.5% with supernumerary mammae. The pectoral region was the seat of variation. "The number of mammae in the inguinal region remained almost constant." Several investigators have mentioned the incidence of supernumerary mammae in rats but have given no data on the degree of incidence or extent of the abnormality. Donaldson[2] reports the normal number as 12 and merely states that there may be as few as 10 or as many as 14.

The normal mammary pattern in mice consists of five pairs of mammae. Three of these are located in linear order in the thoracic region and two in the inguinal as shown in Figure 13*A*. For purpose of description and discussion the pairs are numbered from 1 to 5 proceeding in an anterior to a posterior position.

The best times to observe and to record the mammae are during the lactating period in the adult and at the ten day stage in the young before the nipples are obscured by hair. Observations have been made at both these stages.

Observations

Variations of three types were recorded as follows:

1) *Deficiency in number or function of mammae.*
   a) One less gland on the right side
   b) One less gland on the left side
   c) One less pair
   d) Two less pairs
2) *Supernumerary mammae.*
   a) One more gland on the right side
   b) One more gland on the left side
3) *Positional variation.*
   a) Misplacement of one gland

These may be considered in more detail.

The incidence of abnormalities according to the various stocks is recorded in Table I. Those stocks listed above the horizontal line are inbred in varying degrees. Those below are hybrids which will be discussed later.

Deficiencies

There were recorded three general types of deficiency.

1) The gland had a nipple which, however, appeared to be small and unused. This was the most common type.
2) No nipple could be seen. There was a small milk-white patch under the skin.
3) There was complete absence of all traces of gland or nipple.

The various progressive degrees of deficiency seem to be continuous and a part of the same general process. Various stocks which have been examined with special reference to the extent of the deficiency show different degrees of progress of the process as is shown in Table II.

Since, however, the disuse and reduc-

*This work has been aided by grants to the Roscoe B. Jackson Memorial Laboratory from the Commonwealth Fund, Anna Fuller Fund, International Cancer Research Foundation, Jane Coffin Childs Memorial Fund and the National Advisory Cancer Council.

tion in any mamma or pair of mammae is definitely localized and persists throughout the life of the individual, it is probable that the process which gives rise to the minor degree of deficiency is just as definite and permanent biologically as is that which underlies the more advanced deficiencies. There are ample grounds for basing such a conclusion on an analogy with minute degrees of spotting or of skeletal abnormalities which are just as definitely established genetically as are the more extensive variations of the same type.

The two stocks showing the highest percentages of deficiencies are the *A* and *dba* stocks. The incidence is 7.81% and 7.47% respectively. The tvpe of deficiency is, however, quite different.

A stock. The positions of deficient mammae in this stock is as follows:

R_1	R_2	R_3	R_4	R_5
1	2	18	0	0
L_1	L_2	L_3	L_4	L_5
0	0	18	0	0

There are nine animals with more than one mamma deficient. One of these, ♀ 3-1-196, has two unilateral deficiencies, one in the first right and the other in the third right mamma. The other eight bilateral deficiencies are paired 3rd mammae in each case. It is clear that the tendency to deficiency is located in the 3rd pair of mammae for 36 out of the 39 observed are in that position.

dba stock. The position of deficient mammae in this stock is as follows:

R_1	R_2	R_3	R_4	R_5
1	0	1	1	21
L_1	L_2	L_3	L_4	L_5
1	0	1	1	20

There are 16 animals wth more than one mamma deficient. Of these 13 have two mammae involved and *all* have paired 5th mamma deficiency. One mouse, ♀ 16-3-15, has three, a paired 5th and a 3rd left mamma deficiency. Two animals have four deficiencies—♀ 15-3-10, with paired 1st and 5th mammae and ♀ 15-3-6, with paired 4th and 5th mammae. Forty-one of the forty-seven deficiencies are in this pair of glands. In this stock the deficiency consists in disuse of the 5th pair of mammae rather than absence of the nipple.

Another remarkably interesting and different localization is found in the *C57* stock, its derivative *BBC* and its ancestral relative the leaden stock. In these cases there is a localization in the 2nd pair of mamae as follows:

	R_1	R_2	R_3	R_4	R_5	L_1	L_2	L_3	L_4	L_5
C57 black	0	6	1	0	0	0	8	0	0	0
Leaden	0	2	0	0	0	0	0	0	0	0
BBC	0	1	0	0	0	0	1	0	0	0
Total	0	9	1	0	0	0	9	0	0	0

Eighteen out of 19 deficiencies are on the second pair of mammae. In the *C57* black stock there are four animals with two deficiencies. One of these has 2nd and 3rd right mammae. The other three have paired second mammae. It is also interesting to note that the one case of misplaced mammae in the *BBC* mice involves the third gland which is close to and a little outside of the 2nd mammae. This is shown in Figure 13*B*.

Four other stocks show more than one per cent of deficient animals. These may be tabulated as follows:

	R_1	R_2	R_3	R_4	R_5	L_1	L_2	L_3	L_4	L_5
C3H	0	0	6	0	0	0	0	5	0	0
C	0	0	6	0	0	0	0	3	0	0
Swiss	1	1	13	1	0	1	2	14	0	0
Stock × A	0	0	4	0	0	0	0	4	0	0

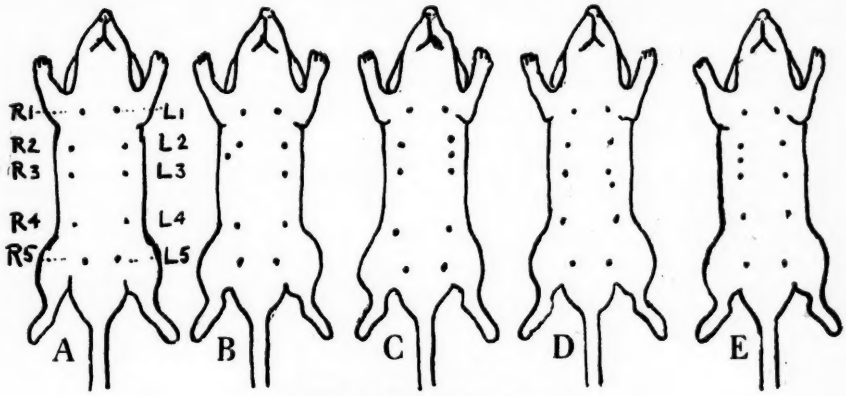
In the *C3H* stock five of the six deficiencies consist of paired 3rd mammae.

In the *C* stock three are paired 3rd mammae.

In the Swiss stock which is least inbred of all the "pure" stocks considered, there is more variation in location of the deficiencies than in any of the others. Thirteen mice have two deficiencies of which 12 are paired 3rd mammae and one paired 1st mammae. One mouse has *five* deficiencies, paired 3rd, paired 2nd mammae and a right 4th mamma.

In all the deficient mice not one that has two deficiencies has them on opposite sides unless they are members of the same pair. This shows that the abnormality is definitely located in a linear order and that it may or may not extend to an opposite mamma as the case may be.

In each stock there is a very charac-



SUPERNUMERARY MAMMAE

Figure 13

A—the normal arrangement of mammae in the mouse with key to designation of location of mammae used in text. *B*—one mamma displaced. *C*, *D*, and *E*—various locations of supernumerary mammae.

teristic localization which is tabulated in Table III.

Transmission of Deficiencies

While there are very characteristic patterns of deficiency for each stock of mice, there is little if any evidence of transmission of the defects from mother to daughter. Any such tendency may well be more evident if crosses are made than by a study within the inbred stock. It is planned to make and study reciprocal crosses involving the *A*, *C57* and *dba* stocks.

Supernumerary Mammae

The *C* strain is the only one in which the incidence of supernumerary mammae is sufficient to allow a quantitative study.

Before considering this strain however we may list the other sporadic cases observed. These are as follows:

Swiss ♀7-318—A supernumerary between mammae L_2 and L_3.
A ♀1-2-25—A supernumerary between mammae L_3 and L_4.
Stock × A ♀5-1-32—A supernumerary mammae L_2 and L_3.

These locations are the same as those observed in the *C* stock.

In the *C* stock 48 mice had supernumerary mammae out of a total of 532 examined. Of these 37 had the extra mamma on the left side, 11 on the right side. *No mouse had more than one supernumerary mamma.* This is a marked contrast to the paired condition found so frequently in deficiencies.

The *C* mice are classified as follows:

Left	between 2 and 3	22	Fig. 13*C*
Left	between 3 and 4	15	Fig. 13*D*
Right	between 2 and 3	11	Fig. 13*E*
Right	between 3 and 4	0	

Thirty-three of the supernumerary mammae were located between the second and third, while 15, *all on the left side,* were located between the third and fourth mammae. Clearly we have some very distinct and significant localization factors involved.

In contradistinction to the deficiencies, the occurrence of supernumeraries appears to be determined by conditions which are distinctly unilateral and which reach a critical stage of activity in a very restricted area.

Transmission of Tendency to Supernumerary Mammae

One group of the F_1 hybrids whose mothers were *C* stock mice and whose fathers were Swiss has been observed. Five of these or 1.96% had supernumerary mammae distributed as follows:

Left between 2 and 3 . . . 4
Left between 3 and 4 . . . 1

Not only did the localization resem-

ble that of their *C* stock mothers but the total incidence was sufficiently great to suggest that interesting genetic studies of this variation may be possible.

Discussion

As evidence for the relative importance of certain non-mendelian influences increasingly invades the field of mammalian genetics, it is useful to study and record the incidence of variations which need further investigation.

Among the organs to which, in rodents, little genetic study has been given the mammary glands are of considerable potential interest.

The present data involving a total of 4,296 mice of eight distinct stocks and some of their hybrids are sufficient to show that variation from the normal number of mamae occurs in both plus and minus directions. The degree of accuracy with which the localization of such variations is determined suggests very definitely that this process is not random, and that morphogenetic factors of distinct identity are involved.

At the same time the relatively low incidence of such variations in material of high genetic uniformity makes it highly probable that some influences other than genes are involved. This does not mean that genes may not provide an essential substrate, but if one argues by analogy with such characters as otocephaly or polydactyly in guinea pigs it seems likely that we may be dealing with complicating but significant influences of other sorts as well.

The relatively slight degree of gene influence on the incidence of mammary tumors in mice as compared with the "milk" influence and with hormonal action provides another reason why further study of the basis for mammary variation is desirable.

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Table I. Number of mice with deficient mamae and with supernumerary mamae.

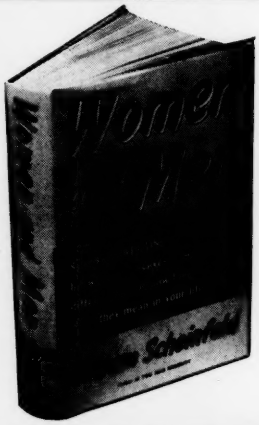
Stock	No. mice examined	Deficient Mamae		Supernumerary Mamae		Misplaced
		No.	%	No.	%	
A	371	29	7.81	1	0.26	0
C	582	6	1.12	48	9.02	0
C3H	139	6	4.31	0	0.00	0
C57blk	523	10	1.91	0	0.00	0
Ce	60	0	0.0	0	0.00	0
dba	348	26	7.47	0	0.00	0
Swiss	1072	17	1.58	1	0.09	0
Leaden	47	2	4.2	0	0.00	0
C/Swiss	254	1	0.39	5	1.96	0
C/SwissXSwiss	45	0	0.00	0	0.00	0
Stock XA	307	7	2.28	1	0.32	1
BBC	700	2	0.28	0	0.00	1

Table II. Analysis of deficient mamae examined.

Stock	No. of deficient mamae examined	No. with absence of nipple	No. showing merely disuse and reduction	%showing absence of nipple
A.	36	27	9	75.0
Swiss	33	27	6	81.8
C3H	11	4	7	36.3
C57 Black	15	5	10	33.3
dba	25	0	25	0.0

Table III. Location of deficient mamae as per cent distribution. (See figure 13 for key)

Stock		% deficiencies according to Pair of Mamae.			
	1	2	3	4	5
A	2.7	0.0	97.3	0.0	0.0
Stock X A	0.0	0.0	100.0	0.0	0.0
C3H	0.0	0.0	100.0	0.0	0.0
C	0.0	0.0	100.0	0.0	0.0
Swiss	6.0	9.0	82.0	3.0	0.0
C57 black	0.0	95.4	6.6	0.0	0.0
Leaden	0.0	100.0	0.0	0.0	0.0
BBC	0.0	100.0	0.0	0.0	0.0
dba	4.2	0.0	4.2	4.2	87.4



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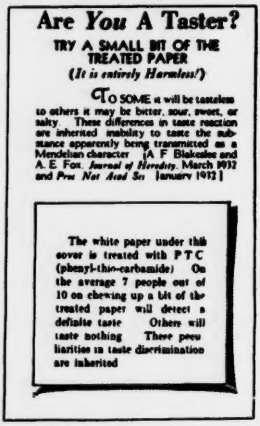
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